Diffuse pulmonary diseases can be classified into two categories:

- **Obstructive (airway) disease**, characterized by limitation of airflow, usually resulting from an increase in resistance caused by partial or complete obstruction at any level, and
- **Restrictive disease**, characterized by reduced expansion of lung parenchyma accompanied by decreased total lung capacity.

The major diffuse obstructive disorders are emphysema, chronic bronchitis, bronchiectasis, and asthma. In obstructive lung diseases, FVC is normal or slightly decreased but FEV1 is significantly decreased.

- By contrast, in diffuse restrictive diseases, FVC is reduced and the expiratory flow rate is normal or reduced proportionately. Hence, the ratio of FEV to FVC is near normal.

- The restrictive defect can be classified as 1) chest wall disorders with normal lungs (severe obesity, diseases of the pleura, and neuromuscular disorders, respiratory muscles) and (2) acute or chronic interstitial lung diseases. The classic acute restrictive disease is ARDS, which was discussed in Pulm Path I.

- Chronic restrictive diseases include the pneumoconioses, interstitial fibrosis of unknown etiology, and most of the infiltrative conditions (e.g., sarcoidosis) and will be discussed in PulmPath III.

### Obstructive Lung Diseases

- Are characterized by 4 prototypical disorders: Asthma, Chronic bronchitis, emphysema and bronchiectasis. Summary of the spectrum of changes seen in these 4 disorders is summarized in Table (see Powerpoint)

- There is some degree of clinical and morphologic overlap between bronchitis, emphysema and asthma.

- It should be noted that the definition of emphysema is on morphologic grounds while chronic bronchitis is primarily a clinical definition. Chronic bronchitis primarily affects large airways while emphysema is a disease of the acinus. However, most of the cases show distinct overlap and in many cases the two entities co-exist,
especially in view of the fact that heavy tobacco exposure is a key etiologic factor for both entities.

- Both entities are clubbed under chronic obstructive pulmonary disease (COPD) and affects 10% of the U.S. adult population and is the fourth leading cause of death in the U.S.

**Emphysema**

- Emphysema is characterized by abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls without significant fibrosis.

- Types of Emphysema:
  - Centriacinar
  - Panacinar
  - Distal acinar
  - Irregular

- Only the first two types cause clinically significant airway obstruction, with centriacinar emphysema being about 20 times more common than panacinar disease.

- Centriacinar (Centrilobular) Emphysema:
  - The central or proximal parts of the acini, formed by respiratory bronchioles, are affected, while distal alveoli are spared.
  - The lesions are more common and severe in the upper lobes, particularly in the apical segments.
  - This type of emphysema is most commonly seen as a consequence of cigarette smoking.

- Panacinar (Panlobular) Emphysema:
  - The acini are uniformly enlarged, from the level of the respiratory bronchiole to the terminal blind alveoli.
  - Occur more commonly in the lower lung zones
  - Occurs in α1-antitrypsin deficiency.

- Distal Acinar (Paraseptal) Emphysema:
  - The proximal portion of the acinus is normal but the distal part is primarily involved (opposite of centriacinar emphysema).
  - Striking adjacent to the pleura, along the lobular connective tissue septa, and at the margins of the lobules.
  - More severe in the upper half of the lungs.
The characteristic finding is the presence of multiple, contiguous, enlarged air spaces ranging in diameter from less than 0.5 mm to more than 2.0 cm, sometimes forming cystic structures referred to as bullae.

- most often in cases of spontaneous pneumothorax in young adults.

**Irregular Emphysema:**
- acinus is irregularly involved,
- is almost invariably associated with scarring, such as that resulting from healed inflammatory diseases.
- most common and clinically asymptomatic

**Pathogenesis:**
- Exposure to toxic substances such as tobacco smoke and inhaled pollutants induces ongoing inflammation with accumulation of neutrophils, macrophages and lymphocytes in the lung.
- Elastases, cytokines (including IL-8) and oxidants are released causing epithelial injury and proteolysis of the extracellular matrix (ECM).
- Unless checked by anti-elastases (e.g., α1-antitrypsin) and antioxidants, the cycle of inflammation and ECM proteolysis continues.
- 80% or more of patients with congenital α1-antitrypsin deficiency develop symptomatic emphysema at an earlier age and with greater severity if the affected person smokes.

- It is also important to remember that genetic factors control response to injury after smoking. For example polymorphisms in the TGF-B gene or polymorphisms in the MMP-9 and MMP-12 genes have been implicated in the pathogenesis.

- On gross examination of emphysematous lungs, the lungs are voluminous and obscure the heart.

- Histologic examination shows enlarged air spaces with destruction of alveolar walls without fibrosis. There is loss of alveolar capillaries as well. Because the elastic tissue is destroyed, there is no traction on the respiratory bronchioles which now collapse during expiration leading to the classic pattern of airflow obstruction on spirometry.
Chronic Bronchitis

The diagnosis of chronic bronchitis is made on clinical grounds and is defined by the presence of productive cough for at least 3 consecutive months for at least 2 consecutive years.

Pathogenesis

- Hypersecretion of mucus, beginning in the large airways.
- Cigarette smoking is the most important cause, other air pollutants, such as sulfur dioxide and nitrogen dioxide, may contribute.
- These environmental irritants induce hypertrophy of mucous glands in the trachea and main bronchi, leading to a marked increase in mucin-secreting goblet cells in the surface epithelium of smaller bronchi and bronchioles.
- In addition, these irritants cause inflammation with infiltration of CD8+ lymphocytes, macrophages, and neutrophils. (Compare and contrast with asthma: which shows a predominant infiltrate of eosinophils)
- Mucus hypersecretion is mediated by local release of T cell cytokines such as IL-13. The transcription of the mucin gene MUC5AC in bronchial epithelium and the production of neutrophil elastase are increased as a consequence of exposure to tobacco smoke.
- Airflow obstruction is because of co-existing chronic bronchiolitis and emphysema
- As seen in gross specimens, the mucosal lining of the larger airways usually is hyperemic and swollen by edema fluid and often covered by a layer of mucinous or mucopurulent secretions.
- On histologic examination, the diagnostic feature of chronic bronchitis in the trachea and larger bronchi is enlargement of the mucus-secreting glands. The magnitude of the increase in size is assessed by the ratio of the thickness of the submucosal gland layer to that of the bronchial wall (the Reid index—normally 0.4). Inflammatory cells, largely mononuclear but sometimes admixed with neutrophils, are frequently present in variable density in the bronchial mucosa.
- Chronic bronchiolitis (small airway disease), characterized by goblet cell metaplasia, mucous plugging, inflammation, and fibrosis, is also
present and maybe associated with complete obliteration of the lumen as a consequence of fibrosis.

Asthma

- Asthma is a chronic inflammatory disorder of the airways that causes recurrent, intermittent but reversible episodes of airway obstruction resulting in wheezing, breathlessness, chest tightness, and cough, particularly at night and/or early in the morning.
- There is chronic bronchial inflammation with eosinophils, bronchial smooth muscle cell hypertrophy and hyperreactivity, and increased mucus secretion.
- Asthma may be categorized into atopic (where there is inflammatory response against environmental antigens) and non-atopic or subclassified based on the agents that trigger bronchoconstriction.
- The major etiologic factors of asthma are genetic predisposition to type I hypersensitivity (atopy), acute and chronic airway inflammation, and bronchial hyperresponsiveness to a variety of stimuli.
- Pathogenesis
  - Type 2 helper T (TH2) cells is critical to the pathogenesis of asthma.
  - Cytokines produced by TH2 cells account for most of the features of asthma—IL-4 stimulates IgE production, IL-5 activates eosinophils, and IL-13 stimulates mucus production and also promotes IgE production by B cells. IgE coats submucosal mast cells, which, on exposure to allergen, release granule contents.
  - This induces two waves of reaction (see powerpoint slide): an early (immediate) phase and a late phase.
  - Repeated bouts of inflammation lead to structural changes in the bronchial wall, collectively referred to as airway remodeling. These changes include hypertrophy of bronchial smooth muscle and mucus glands, and increased vascularity and deposition of subepithelial collagen,
- Complex genetic trait; multiple genes are involved, and multiple environmental factors to initiate a pathologic reaction
Chromosome 5q has several susceptibility genes
- IL 13- genetic polymorphisms susceptibility for atopic asthma
- CD 14 –SNP associated with occupational asthma
- ADAM 33- 20q - member of the metalloproteinase family, polymorphisms accelerate bronchial smooth muscle proliferation

- Morphologically, there is occlusion of bronchi and bronchioles by thick, tenacious mucous plugs, which comprise whorls of shed epithelium (Curschmann spirals). Numerous eosinophils and Charcot-Leyden crystals (collections of crystalloids made up of eosinophil proteins) also are present. Repeated airway inflammation results in basement membrane thickening, smooth muscle hyperplasia.

**Bronchiectasis**

- Bronchiectasis is the permanent dilation of bronchi and bronchioles caused by destruction of the muscle and the supporting elastic tissue, resulting from or associated with chronic necrotizing infections.
- It is not a primary disease but rather secondary to persisting infection or obstruction caused by a variety of conditions.
- Characteristic symptom complex dominated by cough and expectoration of copious amounts of purulent sputum. Diagnosis depends on an appropriate history along with radiographic demonstration of bronchial dilation.
- The conditions that most commonly predispose to bronchiectasis include:
  - Bronchial obstruction
  - Complication of atopic asthma and chronic bronchitis
  - Congenital or hereditary conditions—
    - Cystic Fibrosis
    - Immunodeficiency states
    - Kartagener syndrome
    - Necrotizing, or suppurative, pneumonia, (Staphylococcus aureus or Klebsiella spp., tuberculosis )

**Pathogenesis**
• Two processes are crucial and intertwined: obstruction and chronic persistent infection.
• Normal clearance mechanisms are hampered by obstruction, so secondary infection soon follows; conversely, chronic infection over time causes damage to bronchial walls, leading to weakening and dilation.
• The resultant inflammatory damage to the bronchial wall and the accumulating exudate further distend the airways, leading to irreversible dilation.
• Clinical Features
  ○ severe, persistent cough with mucopurulent sputum.
  ○ Clubbing of the fingers may develop.
  ○ In severe cases: significant obstructive ventilatory defects with hypoxemia and hypercapnia develops
  ○ Complications: pulmonary hypertension, cor pulmonale. Metastatic brain abscesses and reactive amyloidosis
• Pathology: Dilated and ectactic bronchi extending up to the pleural surface. Acute and chronic inflammatory infiltrate within the walls of the bronchi and bronchioles with mucosal ulceration. Long standing cases can result in bronchial wall fibrosis or abscess formation and fungal ball.